UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

EPA United States Environmental Protection Agency **Office of Pesticide Programs**

MEMORANDUM

11/13/2019

SUBJECT: Acute Toxicity Review for *O-Keep anti-mold ecochip*, EPA Reg. No.: 92669-R (resubmission)

FROM: Boris S. Yurchak, Chemist
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TO: Eric Miederhoff / Emilia Oiguenblik
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Registrant: Taiwan OK Bio-Technology Co., Ltd		
Decision No.: 548397	Submission No.: 1029401	E-Sub No.: 35180
DP No.: 452667	Action Code: A500.1	
MRID No(s).: 50472829, 50472830, 50472833, 50472834, 48824105, 50472839, 50472840, 50472843, 50472846,		

Formulation from label			
PC code(s)	CAS #(s)	Active Ingredient(s)	% weight
004901	57-06-7	Allyl isothiocyanate, a.k.a. AITC	0.95
		Other Ingredients	99.05
		Total	100.00

I. BACKGROUND

The Registrant, Taiwan OK Bio-Technology Co., Ltd, has resubmitted an acute 5-pack of toxicity data and 3 waivers to support the Registration of their product: *O-Keep anti-mold ecochip*, EPA Reg. No. 92669-R. The subject product is a Fungistat used to inhabit the mold growth.

The initial submission has been reviewed 8/28/2019 under the same DP number (452667) and was found to be inadequate to characterize the toxicity potential of the proposed product.

The data package included:

1. E-mail from the Registrant, dated 10/31/2019
2. Documents from the initial submission:
    a. Application for pesticide registration, Form 8570-1.
    b. Basic CSF, dated 11/22/2018.
    c. Data matrix, dated 10/29/2018.
    d. Label, undated.

II. FINDINGS/RECOMMENDATIONS

2.1. The proposed product is a sticker, i.e. a piece of paper coated on one side with a pesticide substance. Substrate of the sticker is printing paper, the active ingredient is an oil-like liquid substance, the carrier of the active ingredient is a porous absorbent material glued to the substrate.

2.2. Based on the recommendation of the initial review, the registrant provided the acute toxicity studies conducted for the liquid portion of the product formula.

2.3. The acute oral study provided in MRID 50472829 is unacceptable due to the deviation from the requirements of OPPTS 870.1100. This study contains the summary of the Technical Report conducted by the National Institutes of Health (NIH) in 1982 which was provided under the current submission in MRID 50472830.

The data provided in this summary are questionable. Exactly: clinical observation stated that there were no animal deaths during the course of the study which contradicts with data provided in mortality vs dose table. The table itself is also questionable because it indicates decreasing of mortality with dose increase. The study does not satisfy GLP requirements.

2.4. The acute dermal study provided in MRID 50472833 is unacceptable due to the deviation from the requirements of OPPTS 870.1200. This study cites an article of E.H. Vermont et al. published in Toxicology and Applied Pharmacology, 1977, v.42, pp. 417-423 which was provided in MRID 50472834 under the current submission. No data were provided in MRID 50472833 for mortality, clinical observation and gross necropsy. The study does not satisfy GLP requirements.

However, since the provided estimate of LD50=88 mg/kg corresponds to the most severe Toxicity Category I, the said category can be assigned conditionally to the acute dermal endpoint for regulatory purposes only.

2.5. The acute inhalation study provided in MRID 48824105 is unacceptable due to the deviation from the requirements of OPPTS 870.1300. This study is deemed to be inadequate to characterize the potential acute inhalation toxicity of the proposed product due to significant difference of LC50 estimates obtained by the gravimetric and the analytical methods. Detailed comments are provided in the Data Evaluation Record (DER) of this study.

2.6. The registrant wishes to waive the Primary Eye and Skin irritation studies and is requesting to assign Toxicity Category I for these endpoints (MRIDs 50472839, 50472843). The corresponded waivers are based on the corrosiveness of the pure active ingredient of proposed product to skin (MRID 50472840). The waivers are granted.

Note: The study provided in MRID 50472840 is the Technical Report entitled "Allyl isothiocyanate/3-isothiocyanato-1-propene: *In vitro* Skin Corrosion in the EPISKIN™ Reconstructed Human Epidermis Model". The issuer of the Report is Harlan Laboratories, Ltd, UK. The Agency has not a guideline to review this method.

2.7. In MRID 50472846, the registrant wishes to waive the Dermal Sensitization study based on the corrosiveness of the pure active ingredient of proposed product to skin (MRID 50472840). The waiver is granted with classification of the proposed product as a non-sensitizer.

2.8. The acute toxicity profile of *O-Keep anti-mold ecochip*, EPA Reg. No. 92669-R is as follows:

GRN	Study	MRID	Toxicity Category	Status
870.1100	Acute Oral Toxicity	50472829 50472830	Undetermined	Rejected
870.1200	Acute Dermal Toxicity	50472833 50472834	I	Assigned, Public literature
870.1300	Acute Inhalation Toxicity	48824105	Undetermined	Rejected
870.2400	Primary Eye Irritation	50472839 50472740	I	Waived
870.2500	Primary Skin Irritation	50472840 50472843	I	Waived
870.2600	Dermal Sensitization	50472840 50472846	Non sensitizer	Waived

III. CONCLUSION

The acute toxicity requirements have not been satisfied for the proposed product, EPA Reg. No. 92669-R, for its registration.

IV. PRODUCT LABELING

1. **Signal Word**: Cannot be established due to uncompleted toxicity profile.

2. **PRECAUTIONARY STATEMENTS:** Cannot be prescribed due to uncompleted acute toxicity profile.

Note to PM

The current product is the primary one of a family the same (secondary) products EPA Reg. Nos. 90531-R, 90576-R, 91762-R, 91766-R and 92314-R. Reviews of said (secondary) products are postponed until the final (AD's) decision on the current case is accomplished.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (OCSPP 870.1300)

Product Manager: E. Miederhoff
MRID No.: 48814105

Reviewer: B. Yurchak
Study Completion Date: 8/30/2012
Project No.: 33706

Testing Laboratory: Product Safety Labs
Author: Carolyn Lowe, LATG

Quality Assurance (40 CFR §160): Included

Test Material: *IR9804*, yellow liquid

Concentration: 0.05 mg/L (gravimetric); 0.206 and 0.508 mg/L (analytical)

Chamber Type: Nose-Only Exposure Chamber (ADG Developments LTD)

Animals: Rat, Sprague-Dawley albino strain

Number/Sex: 10 Males and 10 Females (for analytical method)

Age: young adults (9-12 weeks)

Weight: Males: 247-340 g; Females: 176-220 g

Source: Harlan Laboratories, Inc.

Method: Limit Test (OCSPP 870.1300)

Summary:

1. **Estimated LC_{50}:** Undetermined
2. **Mean MMAD, µm:** 1.67/2.18/2.95; **Mean GSD:** 2.35/2.06/2.50
3. **Toxicity Category:** Undermined
4. **Classification:** Not Acceptable

Deviations from Guideline 870.1300 and other comments:

1. Only one Pre-test MMAD measurements were for each exposure level instead of two.
2. Only two test MMAD measurements were conducted for each exposure level instead of four.

3. As per the certificate of analysis (COA, Appendix A of MRID), the test substance contained 99.8% of the active ingredient.

Results:

Amendment to the protocol

At the request of the Sponsor, an initial 0.05 mg/L exposure level was conducted for this study using gravimetric concentration method. Based on the results of the initial exposure and at the request of the Sponsor, a repeat test was performed and the chamber samples collected during each exposure were analyzed using the analytical method for chamber determination. The report reflects the test procedures used for the analytical chamber determination. The data collected from the initial exposure is presented in Appendix C of the MRID.

0.05 mg/L Exposure Level (Initial test, Appendix C)

Following exposure all rats exhibited abnormal respiration, hypoactivity, ano-genital staining, tremors, nasal discharge and/or alopecia on the face. Five males and two females were found dead on Day 2. Two females died by Day 3. All surviving animals showed weight gain thereafter through Day 14. Gross necropsy of the decedents revealed discoloration of the lungs, distention of the stomach and/or intestines and/or a mottled liver. No gross abnormalities were noted for the euthanized animals necropsied at the conclusion of the 14-day observation period.

0.206 mg/L Exposure Level (Appendix B)

Following exposure all rats exhibited abnormal respiration, hypoactivity, ano-genital staining, tremors, ocular and/or nasal discharge. One male was found dead on Day 1 and one female died by Day 2. Apart from eschar from Days 3 through 12 and alopecia on Days 13 and 14 on the nose of one surviving male and female rat, all survivors recovered from all other symptoms by Day 10 and appeared active and healthy for the remainder of the study. Although all rats lost body weight by Day 1 and two males through Day 3, all surviving animals showed weight gain thereafter through Day 14. Gross necropsy of the decedents revealed discoloration of the lungs, distention of the stomach and/or intestines and/or a mottled liver. No gross abnormalities were noted for the euthanized animals necropsied at the conclusion of the 14-day observation period.

0.508 mg/L Exposure Level (Appendix B)

Four males and one female were found dead upon removal from the exposure tubes. Following exposure, the surviving rats exhibited abnormal respiration, tremors, hypoactivity and/or alopecia on the face. A second female was found dead on Day 1 and the fifth male and two additional females died by Day 2. The surviving female recovered from any symptoms by Day

5 and appeared active and healthy for the remainder of the study. Although all surviving rats lost body weight by Day 1, the surviving female showed a continued weight gain thereafter through Day 14. Gross necropsy of the decedents revealed discoloration of the lungs, distention of the stomach and intestines and/or a mottled or darkened liver. No gross abnormalities were noted for the euthanized animal necropsied at the conclusion of the 14-day observation period.

Reported Mortality

Exposure Concentration (mg/L)	Number dead / Number tested		
	Males	Females	Combined
0.05*	4/5	4/5	8/10
0.206	1/5	1/5	2/10
0.508	5/5	4/5	9/10

*) Gravimetrical method

Chamber Atmosphere

Exposure Conc. (mg/L)	Mean MMAD (µm)	Mean GSD
0.053*	1.69	2.35
0.206	2.18	2.06
0.508	2.95	2.50

*) Gravimetrical method

Chamber Environment

Exposure Level (mg/L)	0.05*	0.206**	0.508**
Nominal concentration (mg/L)	0.053	1.31	3.97
Chamber Volume (L)	28****	6.7***	6.7***
Total Airflow Rate (Lpm)	4	30	30
Temperature (°F)	22	22	24-25
Relative Humidity (%)	26-27	26-27	60-62

*) Gravimetrical method
**) Time-weighted average concentration estimated under the analytical method
***) pages 9, 15 of 60
****) page 55 of 60

Based on the analytical method, it was concluded in the study that under the conditions of this study, the 4-hour exposure acute inhalation LC_{50} of *IR9804* (calculated as a Time Weighted Average) appears to be between 0.206 and 0.508 mg/L in male and female rats.

Reviewer's comments

1. As follows from mortality data above, the results obtained from gravimetric and analytical methods differ significantly. The mortality rate is approximately the same (8/10, 9/10) for dose 0.05 mg/L (gravimetric measurement) and 0.508 mg/L (analytical estimate). The difference in doses is approximately 10 times (!). Due to that, the analytical estimate of LC50 equal 0.206 mg/L is questionable. On the other hand, the gravimetrical assessment 0.05 mg/L can not be accepted as a LC50 because there is more than one death per sex at this dose.

2. Last right column in Table 5. ANALYTICAL CHAMBER CONCENTRATIONS is designated as Weighted Average with footnote 3, that listed the formula of calculation. Actually, this column contains RMS errors of Calculated Chamber Concentration provided in the neighbor left column and footnote 3 relies to the note in the bottom of the table "Time-weighted average concentration=…".